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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR                   | ATTORNEY DOCKET NO.                | CONFIRMATION NO.            |
|--|-------------|--|------------------------------------|-----------------------------|
| 10/568,732   | 12/27/2006  | Venkatasubramanian Radhakrishnan Tarur | USV                                | 4931                        |
| 22925 7590 02/04/2009<br>PHARMACEUTICAL PATENT ATTORNEYS, LLC<br>55 MADISON AVENUE<br>4TH FLOOR<br>MORRISTOWN, NJ 07960-7397 |             |  | EXAMINER<br>FIERRO, ALICIA LORETTA |                             |
|  |             |  | ART UNIT<br>4121                   | PAPER NUMBER                |
|  |             |  | NOTIFICATION DATE<br>02/04/2009    | DELIVERY MODE<br>ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@LicensingLaw.net  
administration@LicensingLaw.net

### Office Action Summary

**Application No.**

10/568,732

**Applicant(s)**

TARUR ET AL.

**Examiner**

ALICIA L. FIERRO

**Art Unit**

4121

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) \_\_\_\_ is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-8 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/86)  
Paper No(s)/Mail Date \_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_

## **DETAILED ACTION**

### ***Status of Claims***

1. Claims 1-8 are pending in the instant application, filed February 17, 2006.

### ***Priority***

2. The instant application is a national stage entry of PCT/IN2005/00139, filed May 5, 2005, which claims priority to Indian Patent Application No. 479/MUM/2004, filed May 7, 2004.

### ***Information Disclosure Statement***

3. No Information Disclosure Statement has been filed in the instant application.  
Applicants are reminded of their duty to disclose all information known to them to be material to patentability as defined in 37 C.F.R. 1.56.

### ***Claim Rejections – 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:  

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
5. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim refers to a “preferred base” to be used in the process of claim 1. However,

both steps (a) and (b) in claim 1 utilize a base, which is not necessarily the same in each step.

Applicant must clarify which step of the process in claim 1 the base of claim 2 will be used for.

6. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim refers to a process for preparation which is "substantially described herein." The meaning of this phrase is unclear. The term "substantially" in claim 8 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Additionally, claim 8 makes reference to the "foregoing examples 1 to 2," without listing precisely which examples are being referred to. Claim 8 fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim.

#### *Claim Rejections – 35 USC § 103*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(c), (f) or (g) prior art under 35 U.S.C. 103(a).

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Please note that for the purposes of examination on the merits, all “preferred,” “preferably” and “may be” language of Claims 2-7 was not given patentable weight. Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. See MPEP 2111.04. Thus, the scope of claims 2-7 has been interpreted by the Examiner as the following:

- Claim 2. A process as claimed in claim 1.
- Claim 3. A process as claimed in claim 1(b).
- Claim 4. A process as claimed in claim 1(a), where the organic solvent is selected from alcohols, cyclic ethers, dipolar aprotic solvents and glycol ethers.

- Claim 5. A process as claimed in claim 1(b) where the hydroxylic solvent is water of C<sub>1</sub>-C<sub>4</sub> alcohols.
- Claim 6. A process as claimed in claim 1(a).
- Claim 7. A process as claimed in claim 1(b).

10. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 4,697,022 in view WO 2004/041783.

11. Please note that this rejection of claim 8 is in light of the 35 U.S.C. 112 rejection above as it is unclear precisely which subject matter Applicants intend to claim. The phrase "substantially described herein" has been taken by the Examiner to mean the process described in claims 1-7.

12. Patent document '022 discloses methods of preparation of 4-(2,3-epoxypropoxy)-carbazole (which is prepared via the steps set forth in claim 1(a) of the instant application). See Examples 3 and 4, columns 7-8, lines 30-68 and 1-2, respectively) wherein 4-hydroxycarbazole is reacted with R-(-)-epichlorhydrin in the presence of a base (sodium hydroxide) and in an organic solvent (dimethylsulfoxide). This reaction is carried out at ambient temperature (examples 3 and 4), which is generally recognized by those of ordinary skill in the art as being about 20°C-25°C. The Examiner asserts that the temperature conditions in these examples meet the limitations of those set forth in instant claim 1(a). The '022 document additionally teaches that 4-(2,3-epoxypropoxy)-carbazole is capable of reacting with a methoxyphenoxyethylamine compound, namely o-methoxyphenoxyethylamine, to form Carvedilol, a known pharmaceutically active substance (Examples 7 and 8). Said process is not

carried out in the presence of a base or with a salt of the methoxyphenoxyethylamine, causing it to differ from this instantly claimed process in claim 1(b).

13. The reference differs from the instant claims insofar as it does not specifically teach the method of preparing Carvedilol from 4-(2,3-epoxypropoxy)-carbazole that is disclosed in instant claim 1(b). The examples given in '022 which are relevant to instant claim 1(b) (Examples 7 and 8) do not teach the use of a base for the process of producing Carvedilol from its intermediate [4-(2,3-epoxypropoxy)-carbazole], the use of a salt of 2-(2-methoxyphenoxy) ethylamine, nor do they specify the temperature conditions under which said reaction is carried out.

14. WO 2004/041783 (hereafter referred to as '783 document) teaches a method of producing Carvedilol which meets all limitations of instant claim 1(b). In the presence of a base (which the reference teaches as an alkali or alkaline earth metal carbonate) and an organic solvent (which the reference teaches as C2-C5 alcohols, which are all examples of hydroxylic solvents), 4-(oxirane-2-ylmethoxy)-9H-carbazole is reacted with salts of 2-(2-methoxyphenoxy)ethylamine. Please note that 4-(oxirane-2-ylmethoxy)-9H-carbazole in the '783 document has a structure identical to that of 4-(2,3-epoxypropoxy)-carbazole in the instant application. In Example 1 of the '783 document, 4-(oxirane-2-ylmethoxy)-9H-carbazole is added to a mixture of 2-(2-methoxyphenoxy)ethylamine hydrogenchloride monohydrate and anhydrous potassium carbonate in isopropanol. The reaction mixture is heated at 83°C for 5 hours. Additionally, the specification of '783 teaches that the use of a 2-(2-methoxyphenoxy)ethylamine salt, in comparison with its basic form, makes the reactant more stable and available without raising the cost of producing Carvedilol. Finally, the Applicants in the '783 document disclose that the method taught by this document to produce Carvedilol lowers the contamination of the final

product with its bis-derivative. Thus, the use of a base in the disclosed process of preparing Carvedilol along with the use of a salt of 2-(2-methoxyphenoxy)ethylamine are beneficial to the synthesis of Carvedilol in several ways, including lowering the cost, increasing stability, and decreasing contamination.

15. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to combine the method of preparing 4-(2,3-epoxypropoxy)-carbazole taught by '022 with the subsequent method of using said compound to produce Carvedilol disclosed in '783 because it is well known in the art that 4-(2,3-epoxypropoxy)-carbazole is capable of reacting with a methoxyphenoxyethylamine compound, such as the one disclosed in instant claim 1(b) to form Carvedilol, a known pharmaceutically active substance. The motivation to do so is drawn from a combination of the '022 and '783 references. As stated in paragraph 9 above, '022 teaches the production of Carvedilol from 4-(2,3-epoxypropoxy)-carbazole and o-methoxyphenoxyethylamine. Additionally, the '783 document teaches that using a salt of 2-(2-methoxyphenoxy)ethylamine instead of the basic form of the compound makes it more stable and readily available without increasing the cost of Carvedilol production. Additionally, products prepared by utilizing the method in the '783 document has up to three times lower contents of the bis-derivative of Carvedilol, which in turn increases the purity. Thus, it would be *prima facie* obvious to combine these two references with a reasonable expectation of success.

### ***Conclusion***

16. No claims are allowed.



17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALICIA L. FIERRO whose telephone number is (571)270-7683. The examiner can normally be reached on Monday - Thursday 6:00-4:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AF

/Patrick J. Nolan/  
Supervisory Patent Examiner, Art Unit 4121